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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/407,430	09/29/99	WORMAN H	0575/54805

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JOHN P WHITE
COOPER & DUNHAM LLP
1185 AVENUE OF THE AMERICAS
NEW YORK NY 10036

EXAMINER	
NGUYEN, Q	
ART UNIT	**PAPER NUMBER**
1632	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/407,430	WORMAN ET AL.	
	Examiner	Art Unit	
	Quang Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 August 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,7 and 9-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,7 and 9-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11,13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's amendment filed August 17, 2001 in Paper No. 12 has been entered. Amended claims 1, 3, 5, 7 and 9-11 are pending in the present application, and they are examined on the merits herein.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior office action.

Written Description

Amended claims 1, 3, 5 and 10-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action in Paper No. 10 (pages 4-6).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of

ordinary skill in the art to recognize that [he or she] invented what is claimed."Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

Applicant's invention is drawn to a method of treating or preventing hepatitis C virus (HCV) infection in a subject using an effective amount of an E_0 protein to the subject, wherein the E_0 protein is capable of inhibiting the attachment of hepatitis C virus onto cells by specifically binding to the hepatitis C virus envelope E2 protein, so as to treat or prevent hepatitis C virus infection. In analyzing whether the required written description is met for genus claims, it is first determined whether a representative number of species has been described by their complete structure. Apart from the disclosure that a portion of a protein of unknown function that has a sequence of SEQ ID NO: 1, and its fragment containing the amino acid sequence of residues 1-120 of SEQ ID NO:1 are capable of interacting with a portion of hepatitis C virus envelope protein E2, as indicated by the results derived from the yeast two-hybrid assay, the instant specification fails to teach a sufficient number of species of E_0 protein which is not necessarily limited only to SEQ ID NO:1 or its fragment, that are capable of interacting with a portion of hepatitis C virus envelope protein E2, and thereby inhibiting the attachment of hepatitis C virus envelope E2 protein onto cells so as to treat or prevent hepatitis C virus in the method as claimed. Apart from the common functional activity of inhibiting the attachment of heptatitis C virus onto cells, the specification fails to disclose the relevant common core structures shared among these species of E_0 protein. Nor does the prior art at the effective filing date of the present application provide such teachings. The claimed invention as a whole is not adequately described

if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants' filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of the broadly claimed genus of E_o protein having the desired functional property, other than the protein of SEQ ID NO: 1 and its fragment containing the amino acid sequence of residues 1-120, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Responses to Arguments

Applicants' argument related to the above rejection in the Amendment filed on August 17, 2001 in Paper No. 12 (pages 3-6) has been fully considered.

Applicants argued that the subject specification does disclose and does contain a written description of the E_0 protein and its fragment of 120 residues E_o1, and therefore the rejection on written description grounds does not apply to the amended claims, and should be withdrawn. Examiner respectfully finds Applicants' argument to be unpersuasive because although it is true that the instant disclosure discloses and contains a written description of the E_0 protein having SEQ ID NO: 1 and its fragment of 120 residues E_o1, however it does not provide written description or support indicating that Applicants have in possession of a representative number of species for a broad genus of E_0 protein that is capable of inhibiting the attachment of hepatitis C virus onto cells, wherein the E_0 protein is not necessarily limited to SEQ ID NO:1 or its fragment of 120 residues E_o1.

Accordingly, amended claims 1, 3, 5 and 10-11 remain rejected under 35 U.S.C. 112, for lack of Written Description for the reasons set forth above.

Claims 1, 3, 5, 7 and 9-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention the same reasons set forth in the previous Office Action in Paper No. 10 (pages 6-13).

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The claims are directed to a method of treating or preventing hepatitis C virus (HCV) infection in a subject comprising administering an effective amount of an E_0 protein to the subject, wherein the E_0 protein is capable of inhibiting the attachment of hepatitis C virus onto cells by specifically binding to the hepatitis C virus envelope E2 protein so as to treat or prevent hepatitis C virus infection.

The specification teaches by exemplification that using the yeast two hybrid assay, two clones encoding a portion of a protein were selected from a library of human liver Matchmaker cDNA for interacting with a portion of hepatitis C virus E2 lacking its most hydrophobic, carboxyl terminal domain. The sequence of the encoded portion of a protein, referred to as E_o protein, has the amino acid sequence of SEQ ID NO: 1. Furthermore, the specification teaches that the encoded amino acid sequence containing amino acid residues 1-120 of SEQ ID NO:1 (or E_o1 protein) is also capable of binding to the portion of hepatitis C virus E2 as does the E_o protein of SEQ ID NO:1, although at a relatively weaker binding affinity (See specification, pages 18-20).

The above evidence has been noted and considered. However, the evidence can not be reasonably extrapolated to the instant claimed invention which is drawn to a

method of treating or preventing hepatitis C virus infection in a subject using an effective amount of E_0 protein, not necessarily limited to SEQ ID NO:1 and its fragments that are capable of inhibiting the attachment of hepatitis C virus onto cells.

The instant specification is not enabled for the claimed invention because it fails to provide any guidance regarding the use of any E_0 protein, including the E_0 protein that has SEQ ID NO:1 and its fragments, to inhibit the attachment of hepatitis C virus onto cells to treat or prevent hepatitis C virus infection in a subject. The specification fails to teach or demonstrate a correlation or a nexus between the binding interaction of the E_0 protein having SEQ ID NO:1 and the $E_0$1 proteins with a portion of the hepatitis C virus E2 envelope protein observed via the yeast two hybrid assay with any of the therapeutic effects contemplated by the claimed invention which comprise the inhibition of HCV replication, stopping or delaying the progression of liver disease in a subject. Since the prior art at the filing date of the present application does not provide such guidance, it is incumbent upon the instant specification to do so. At the filing date of the present application, standard treatments for patients infected with hepatitis C include therapies using recombinant alpha interferon alone or in combination with the nucleoside analogue Ribavirin, whose actions are not mediated via inhibiting the attachment of hepatitis C virus onto cells (Gish, Seminars in liver disease 19 (S1): 35-47, 1999). Moreover, the physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense

> that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictagle factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Given the lack of guidance provided by the instant specification, it would have required undue experimentation for one skilled in the art to make and use the instant claimed invention.

With regard to broad claims encompassing the use of any E_o protein that is capable of inhibiting the attachment of hepatitis C virus onto cells for the treatment or prevention of hepatitis C virus infection in a subject via any and all routes of administering into the subject, the specification fails to provide any specific relevant information regarding to the effective amount of the protein or its fragments or variants to be used, the route of delivery utilized, the specific regimens deployed such that any therapeutic effect could be achieved in a subject as claimed. Apart from disclosing in the present application that the E_o protein having SEQ ID NO:1 and its fragment E_o1 protein (1-120 of SEQ ID NO:1) are capable of binding to a portion of the hepatitis C virus E2 envelope protein, it is already known in the art that other polypeptides such as the CD81 protein (Abrignani et al., WO 99/18198; see page 2, lines 18-25), annexin V, tubulin, apolipoprotein B (Maertens et al., WO 99/24054; see abstract), as well as endogenous host proteins such as the chaperone protein calnexin and lactoferrin are also capable of binding at least to the hepatitis C virus envelope protein E2 (Maertens et al., WO 99/24054; page 2, lines 12-29). However, the potential therapeutic values of these proteins for treating or preventing HCV infection in a subject remain to be determined or investigated because the mechanism by which HCV enters target cells

remains unknown (Flint et al., J. Virol. 73:6782-67900, 1999; page 6782, column 2, last three lines) and the exact role of HCV envelope proteins E1 and E2 has not yet been elucidated (Maertens et al., WO 99/24054; page 2, lines 12-14). Flint et al. stated that "Clearly, it will be important to demonstrate whether CD81, either alone or with additional factors, can function as the HCV receptor in allowing pseudotyped virus-cell attachment and entry. Since CD81 is so widely expressed, it is unlikely to be the sole factor determining HCV liver tropism" (page 6789, column 1 lines 1-6).

With respect to the use of any E_o protein and its variants in the method as claimed, it is unclear whether these proteins are capable of exhibiting a binding affinity for the full-length E2 envelope protein presented on the surface of the hepatitis C virus, usually in complexes with other viral envelope components, such as the E1 envelope protein. Additionally, it is unclear whether their binding affinity is strong enough to compete efficiently with yet known cellular receptor(s) of HCV and thereby inhibiting the attachment of HCV onto target cells. Gish noted that the standard management of chronic HCV infection is complicated by various factors, including: the rapid mutation rate of the HCV genome, particularly the hypervariable region, the lack of neutralizing antibodies to HCV gene products, and the lack of sequence homology (less than 72%) among various subtypes of HCV (page 36, column 1, first full paragraph, line 8 continues to the first paragraph on column 2). It is thought that the binding of E2 to target cells mostly involves the highly variable amino terminus of E2, the hypervariable region I (Maertens et al., WO 99/24054; page 2, lines 12-17). In view of this, it is further unclear whether any E_o protein, including one that has SEQ ID NO:1 and the E_o1

protein, is capable of binding efficiently *in vivo* to the highly variable region of E2 in any HCV subtype so that to inhibit the attachment of HCV to cellular receptors and thereby treating and preventing HCV infection in a subject. Therefore, given the complete lack of guidance provided by the instant specification regarding to the effective *in vivo* use for any E_o protein that is capable of inhibiting the attachment of hepatitis C virus onto cell so as to treat and prevent HCV infection in a subject, it would have required undue experimentation for a skilled artisan to make and use the claimed invention.

The instant broad claims also encompass any variants of E_o and E_o1 proteins. However, the instant specification offers no guidance as to which region of the E_o protein having SEQ ID NO:1 or E_o1 protein, would be tolerant to alteration and which would not, which "particular" amino acid changes (substitution, deletion or insertion) at which position and at which combinations, such that the variant proteins still possess the ability to bind to HCV E2 protein to inhibit the attachment of hepatitis C onto cells, let alone any E_o protein. It is well recognized in the art, any modification (even a "conservative" substitution) to a critical region of a protein is likely to significantly alter its functional properties. Therefore, there is a high degree of unpredictability associated with the make and use of the claimed embodiment. For examples, in discussing peptide hormones, Rudinger has stated that "The significance of particular amino acids and sequences for different aspects of biological activity can not be predicted a priori but must be determined from case to case by painstaking experimental study (Page 6, first sentence of Conclusions *In* J.A. Parsons, ed. "Peptide hormones", University Park Press, 1976). This unpredictability is further underscored by the fact that the

relationship between the sequence of a peptide and its tertiary structure (or its activity), for this instance the ability to bind to HCV E2 protein, is not well understood and is not predictable (Ngo et al., *In* K. Merz et al., ed. "The protein folding problem and tertiary structure prediction", Birkhauser, 1994, 491-495). Again, in the absence of any guidance provided by the instant specification showing the effectiveness of any E_o or E_o1 variant protein in treating or preventing HCV infection in a subject, it would have required undue experimentation for one skilled in the art to make and use the instantly claimed invention.

The instant claims encompass any and routes of administering the E_o protein into a subject to treat or prevent hepatitis C infection. However, the instant specification fails to provide any relevant information regarding to the *in vivo* stability of the E_o protein utilized or how to overcome random degradation of the administered E_o protein in a treated host and more importantly how to target the E_o protein to a desired tissue or organ in an effective amount by any and all means of delivery such that any therapeutic effects (treatment and prevention) contemplated by Applicants could be attained for the method as claimed. Again, in the absence of any guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the claimed invention.

Accordingly, due to the lack of guidance provided by the specification regarding to the issues set forth above, the state of the art on treatment or prevention of hepatitic C at the effective filing date of the present application, the unpredictability of the

physiological art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant claimed invention.

Responses to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on August 17, 2001 in Paper No. 12 (pages 6-10) have been fully considered.

Applicants mainly argued that in light of the study of Rosa et al. (PNAS 93:1759-1763, 1996; Exhibit 14) indicating that E2 envelope protein of HCV can bind to the plasma membranes of cells and this action of E2 mediates entry of the virus into the cells, together with the study of Yi et al. (Virology 231: 119-129, 1997, Exhibit 17) showing that E2 and E1 envelope proteins form a heteromeric complex and this complex is necessary for virus binding to the cells and entry into the cells, it is therefore reasonable to expect that the E_o protein of the present invention to block HCV attachment and entry into cells due to its capability to bind E2 envelope protein. Applicants further argued that when taken together with the knowledge available at the filing date of the subject invention, the disclosed experiments are reasonably correlated with the method as claimed. Examiner respectfully finds Applicants' arguments to be unpersuasive for the following reasons.

Firstly, there is no evidence of record (*in vitro* or *in vivo*) indicating that any E_o protein of the present invention is capable of binding to the same E2 envelope protein epitopes that are thought to be responsible for cell attachment. Nor is there any evidence of record (*in vitro* or *in vivo*) indicating that any E_o protein of the present

invention is capable of disrupting the formation of the E1 and E2 heteromeric complex that is thought to be necessary for HCV virus binding and entry to the cells.

Secondly, at the filing date of the present application the mechanism by which HCV enters target cells remains unknown (Flint et al., J. Virol. 73:6782-67900, 1999; page 6782, column 2, last three lines) as well as the exact role of HCV envelope proteins E1 and E2 has not yet been elucidated (Maertens et al., WO 99/24054; page 2, lines 12-14). This is also supported by the instant specification which states that "The hepatitis C virus envelope proteins E1 and E2 interact with hepatocyte plasma membrane proteins that likely mediate the entry of the virus into cells.....E1 and E2 may form a heteromeric complex and their association may be necessary for virus binding to cells and for their entry into cells. However cell surface proteins that function as hepatitis C virus receptors or co-receptors by binding to E1 and E2 have not been identified." (page 3, lines 15-24). Furthermore, also at the filing date of the present application, standard treatments available for patients infected with hepatitis C include therapies using recombinant alpha interferon alone or in combination with the nucleoside analogue Ribavirin, whose actions are not mediated via inhibiting the attachment of hepatitis C virus onto cells (Gish, Seminars in liver disease 19 (S1): 35-47, 1999). Therefore, in view of the state of the art at the filing date of the present application, the mere disclosure that the E_o protein having SEQ ID NO:1 and the E_o1 protein that are capable of interacting with a portion of the hepatitis C virus E2 envelope protein observed via the yeast two hybrid assay, is not deemed to be sufficient guidance or a reasonable correlated example for a method of treating or preventing hepatitis C

virus infection in a subject by administering an effective amount of any E_o protein into said subject. With the lack of guidance provided by the present disclosure, it would have required undue experimentation for a skilled artisan to make and use the method as claimed.

Thirdly, with respect to the breadth of the instant claims (e.g., any route of administration, any E_o protein and/or its variant and fragment, to treat any hepatitis C subtype), Applicants failed to address the issues that were raised in the previous Office Action. Given the disclosure of the present invention, it would have required one skilled in the art undue experimentation to practice the method as claimed.

Accordingly the amended claims 1, 3, 5, 7 and 9-11 remain rejected under 35 U.S.C. 112, first paragraph, for the same reasons set forth above.

Conclusions

Claims 1, 3, 5, 7 and 9-11 are free of prior art. At the time of the instant invention, the prior art did not teach or fairly suggest a method of treating or preventing hepatitis C virus infection in a subject using an effective amount of an E_o protein that is capable of inhibiting the attachment of hepatitis C onto cells by specifically binding to the hepatitis C virus envelope E2 protein as claimed.

No claims are allowed.

DAVE T. NGUYEN
PRIMARY EXAMINER

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136 (a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136 (a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Karen Hauda, at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Patsy Zimmerman, whose telephone number is (703) 308-0196.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Quang Nguyen, Ph.D.